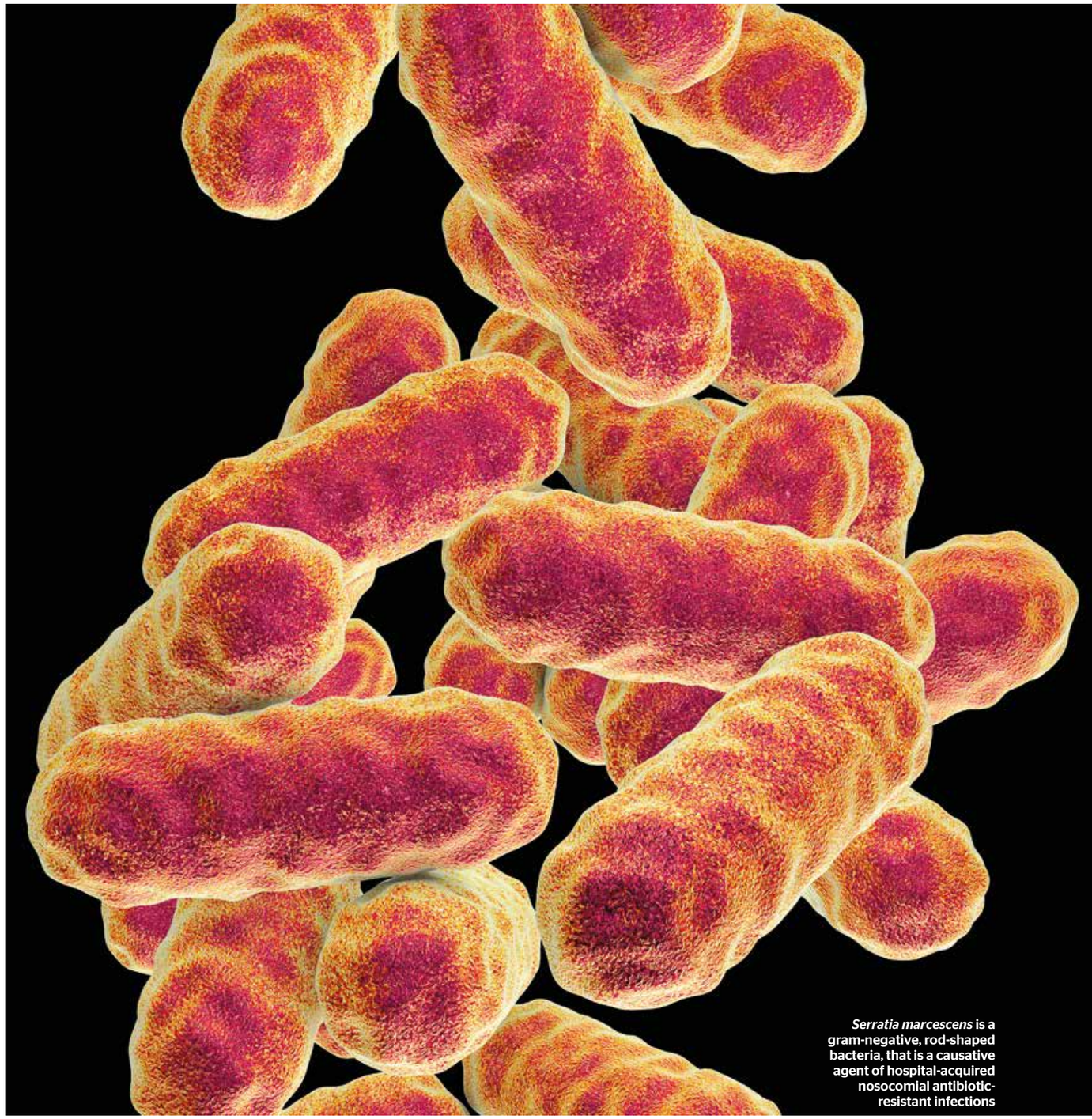
THE PATH OF LEAST RESISTANCE

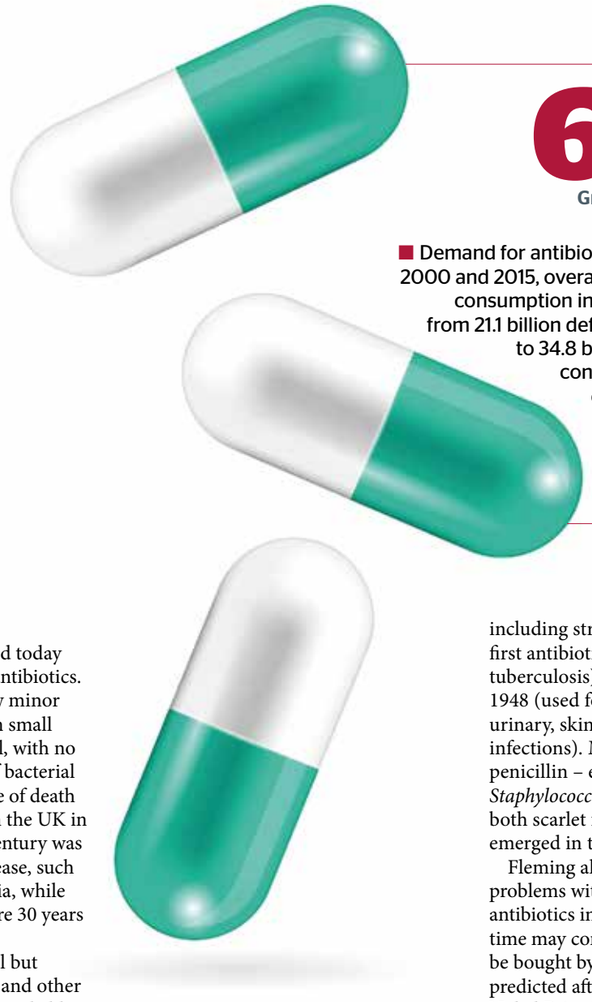
Antimicrobial resistance threatens to become the world's largest health hazard as antibiotics become ineffective through overuse, potentially reversing years of development progress. Can this crisis be averted?

by Chris Fitch
Maps by Benjamin Hennig



SHUTTERSTOCK

Serratia marcescens **is a gram-negative, rod-shaped bacteria, that is a causative agent of hospital-acquired nosocomial antibiotic-resistant infections**



65%

Growth rate of worldwide antibiotic consumption

■ Demand for antibiotics is soaring. Between 2000 and 2015, overall worldwide antibiotics consumption increased by 65 per cent, from 21.1 billion defined daily doses (DDD), to 34.8 billion DDDs. If this trend continues, global antibiotic consumption in 2030 is estimated to be more than double, at 128 billion DDDs.

Few people around today could recall a world before antibiotics. The pre-antibiotic world saw minor surgery, childbirth, and even small cuts become potentially fatal, with no way to prevent the spread of bacterial infections. The leading cause of death in almost every age group in the UK in the early years of the 20th century was some form of infectious disease, such as tuberculosis or pneumonia, while average life expectancies were 30 years shorter than they are today.

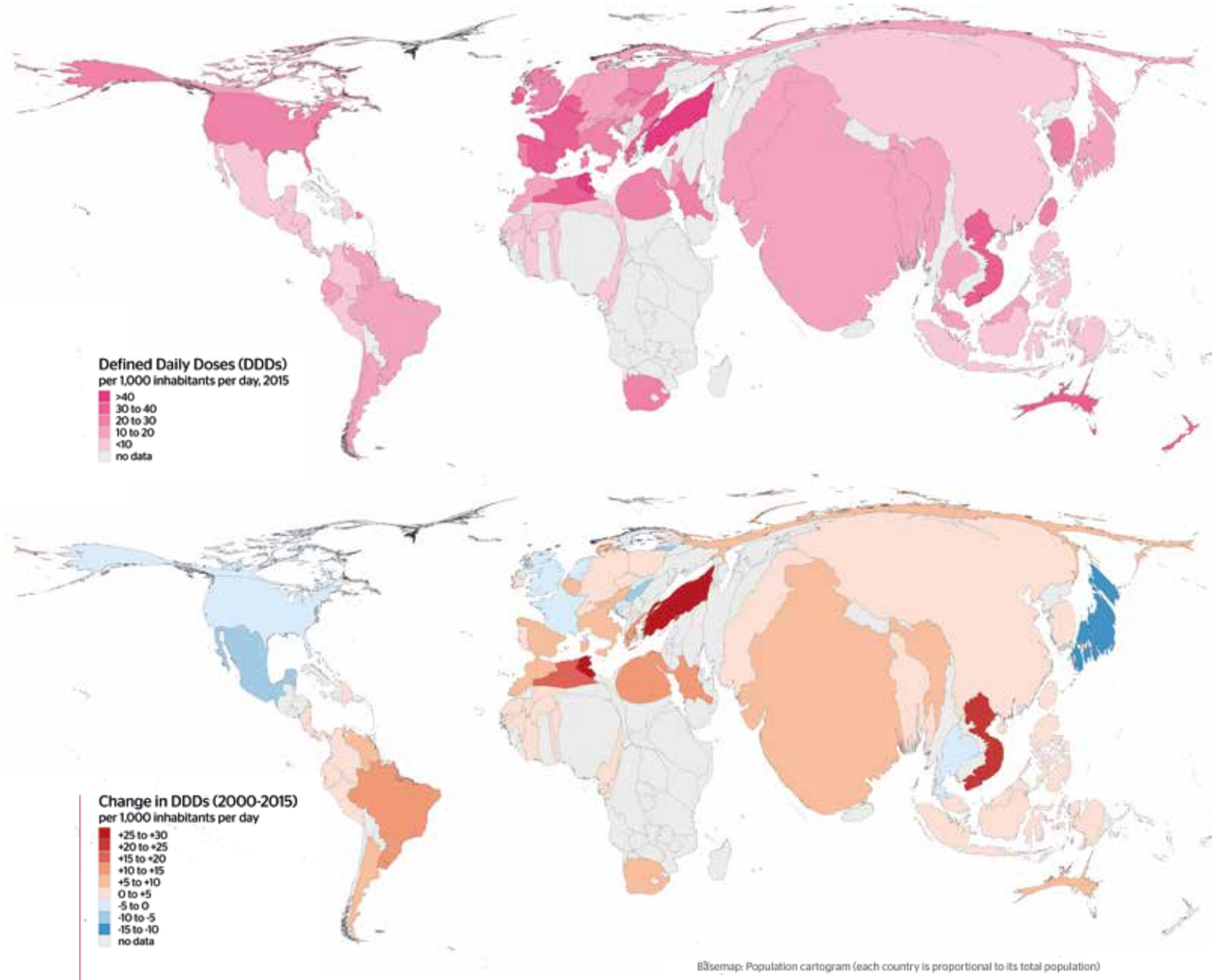
Today, these threats are all but vanished, at least in the UK and other developed societies. It's a remarkable development given that it's been only 90 years since bacteriologist Alexander Fleming stumbled upon something strange in his lab at St. Mary's Hospital Medical School. Famous for leaving bowls full of bacteria cultures lying around his workstation, in September 1928 Fleming discovered that a fungus from the *Penicillium* family had contaminated one of his experiments, inhibiting the growth of the bacteria he was studying. When he identified and isolated the chemical responsible, he named it 'penicillin' in tribute. It was the world's very first antibiotic. Since Fleming made that breakthrough, a wave of revolutionary antibiotics quickly joined the medical arsenal, including streptomycin in 1943 (the first antibiotic capable of treating tuberculosis) and the cephalosporins in 1948 (used for a number of respiratory, urinary, skin, bone, joints, and blood infections). Meticillin, a derivative of penicillin – effective against various *Staphylococcus* infections, as well as on both scarlet fever and pneumonia – emerged in the 1950s.

Fleming also foresaw potential problems with the effectiveness of antibiotics in the long-term. 'The time may come when penicillin can be bought by anyone in the shops,' he predicted after accepting his shared Nobel Prize in Physiology or Medicine in December 1945. 'Then there is the danger that the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug, make them resistant.' He posed a curious hypothetical situation where a 'Mr X' takes penicillin to fight a sore throat, but fails to take enough to kill the infection, and instead just makes it resistant, a situation which subsequently leads to the death of his wife, Mrs X, when penicillin is no longer capable of curing her pneumonia. 'Moral: If you use penicillin, use enough,' he insisted.

Environmental pollution

■ Wastewater and sewage – especially from medical facilities and farms – are rising on the agenda as a source of antimicrobial resistance, even in low concentrations. 'Most research efforts to tackle this has been around reducing clinical prescribing, but we now know that the environment is likely to play a part in how resistance to antibiotics can evolve and spread,' says William Gaze, associate professor at the University of Exeter's Medical School. 'We all need to think more holistically about environmental management of waste, including how we treat our waste water.'

The problem is further complicated by recent research that shows that even common non-antibiotics can contribute towards AMR when released into the environment in large quantities. 'These chemicals are used in much larger quantities at an everyday level, so you end up with high residual levels in the wider environment, which can induce multi-drug resistance,' explains Dr Jianhua Guo from the University of Queensland's Advanced Water Management Centre. Guo studied triclosan, a compound found in thousands of home toiletries, including toothpaste and hand wash, and confirmed that it contributed towards resistance in *E. coli*. 'This discovery provides strong evidence that the triclosan found in personal care products that we use daily is accelerating the spread of antibiotic resistance.'



Global distribution and change in antibiotic consumption

■ A recent study on the changing geographical patterns in antibiotic consumption highlighted the problem of antibiotic resistance becoming a global issue. In low- and middle-income countries an increase in antibiotic consumption in the past 15 years (2000 to 2015) was observed to be correlated with growth in GDP. This correlation does not exist in high-income countries which already have high levels of consumption. Here consumption was observed to even go down slightly in some countries. These two cartograms show why this is affecting global resistance patterns with growing amounts of people in low- and middle-income countries consuming more antibiotics. At the same time are prevailing inequalities in health, a reason for an increase in consumption in these countries. The maps also highlight the need for more concerted efforts to globally monitor antibiotic consumption so that more effective policies can be developed. Such policies must not only tackle the issue of antibiotic resistance, but allow for the development of alternative strategies to reduce the underlying health problems that lead to that increase in antibiotic consumption.

GROWING THREAT

Despite Fleming's warnings, this hypothetical scenario is increasingly proving prophetic. Antibiotic resistance (or antimicrobial resistance, AMR, the more broad-strokes term) is on the rise. 'Antibiotics really underpin most aspects of 20th century medical development,' emphasises Dr Liz Tayler, technical officer at the World Health Organization. 'What is happening with resistance is those drugs are becoming less effective and more expensive, with more treatment failure. That is why AMR is such a risk.'

Data from the WHO's very first Global Antimicrobial Surveillance System (GLASS), aiming to provide a universal global mechanism for tracking cases of resistance, revealed over 500,000 cases of suspected antimicrobial resistance across the 22 countries that submitted data in 2016. In the worse cases, as many as 80 per cent of patients showed signs of resistance to certain antibiotics (these figures do not include tuberculosis, which is measured separately and saw 490,000 people develop resistance). Cases of antimicrobial resistant gonorrhoea and syphilis have been

confirmed across Europe and in other developed countries including Australia and Canada. The fight against malaria is also increasingly being complicated by rising resistance in Southeast Asian countries such as Cambodia, Thailand and Vietnam.

'Antibiotic resistance is a global crisis that we cannot ignore,' announced Tedros Adhanom Ghebreyesus, director-general of WHO, in November 2017. 'If we don't tackle this threat with strong, coordinated action, antimicrobial resistance will take us back to a time when people feared common infections and risked their lives from minor surgery.'

These strong words weren't the first such warning. In September 2016, the UN General Assembly passed Resolution 71/3, acknowledging, among other things, that 'owing to antimicrobial resistance, many achievements of the 20th century are being gravely challenged, in particular, the reduction in illness and death from infectious diseases achieved through social and economic development'.

The UN's World Antibiotic Awareness Week has been held every November since 2015, aspiring to raise awareness of the issue, while then world leaders Barack Obama and David Cameron both made tackling the crisis a priority back in 2014, each launching separate initiatives to incentivise new solutions.

The imminent threat of AMR was laid out in the *Review on Antimicrobial Resistance* commissioned by Cameron, chaired by Lord Jim O'Neill, and sponsored by the Wellcome Trust and the UK Department of Health. 'We estimate that by 2050, ten million lives a year and a cumulative $100trillion of economic output are at risk due to the rise of drug resistant infections if we do not find proactive solutions now to slow down the rise of drug resistance,' it stated upon publication in May 2016, 'and even today, 700,000 people die of resistant infections every year.' O'Neill's co-authored book, *Superbugs: An Arms Race against Bacteria*, published earlier this year, builds upon these numbers with new research that suggests AMR could already be responsible for 1.5 million premature deaths annually.

LOSING BATTLES

Broadly, the reasons for these dire predictions are exactly as Fleming feared. Overuse and improper use of antibiotics has enabled the few bacteria that survive (due to various mutations) to multiply steadily, resulting in more and more antibiotic-resistant bacteria. Entirely new infections are now emerging that medical professionals find themselves increasingly unarmed against. 'We're seeing resistance developing as soon as we start using antibiotics a lot,' outlines Tayler.

> In the US, more people died in 2005 from MRSA infections (18,000) than from HIV/AIDS (17,000)

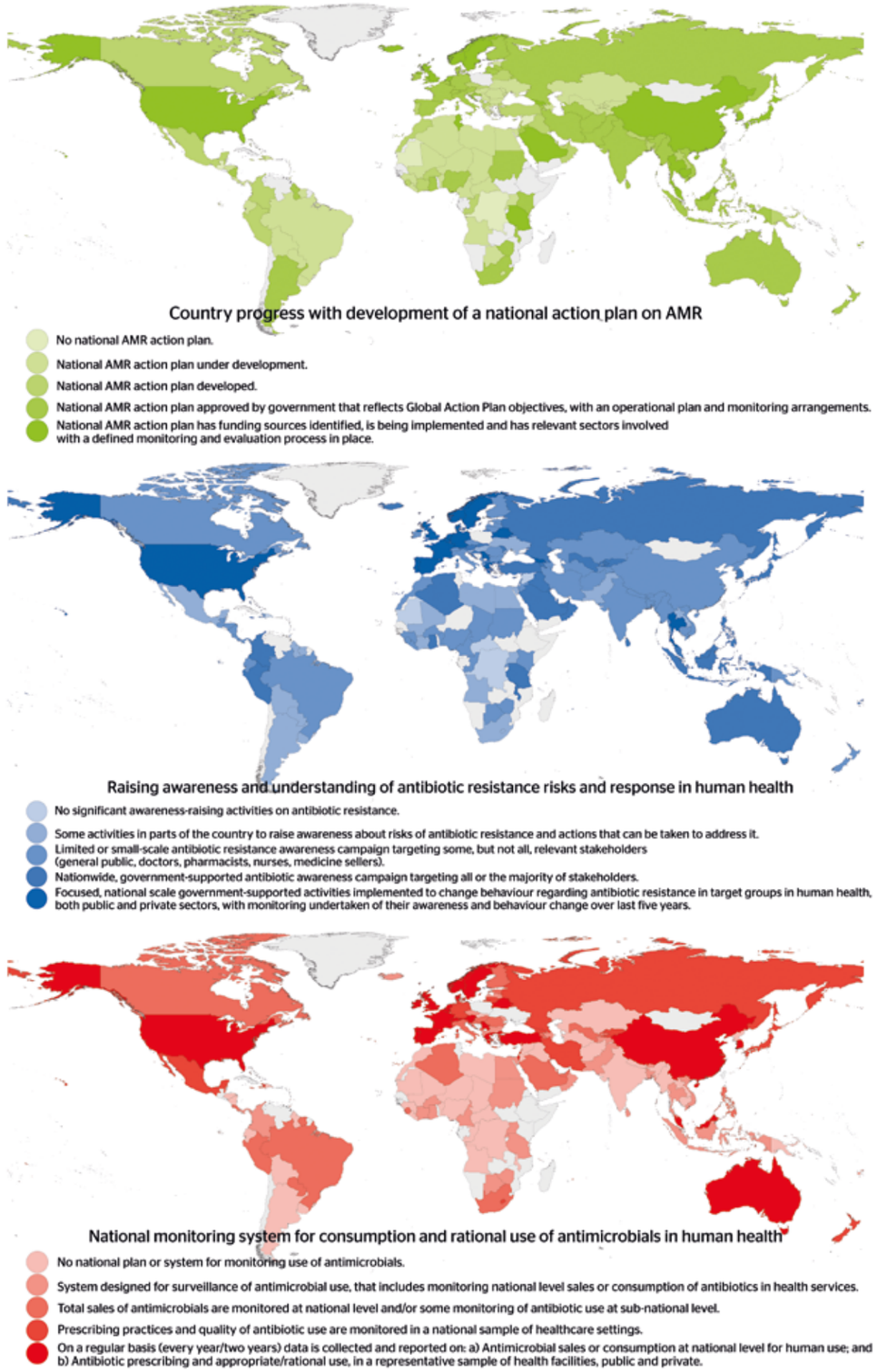
The consequences of this are, to UK audiences, perhaps best understood through newspaper headlines regarding hospital outbreaks of 'superbugs' such as MRSA (methicillin-resistant *Staphylococcus aureus*). Since first emerging in the 1960s, as many as 50 million people are now believed to carry MRSA worldwide, an infection that refuses to react to the once-effective methicillin. In the US, more people died in 2005 from MRSA infections (approximately 18,000) than from HIV/AIDS (approximately 17,000).

The medical industry's response, to selectively treat MRSA with vancomycin, an antibiotic made available for clinical usage in 1958, was inevitably followed by the rise of VRSA (vancomycin-resistant *Staphylococcus aureus*). It's a perfect illustration of how bacteria can mutate and multiply to render once-powerful antibiotics ineffective.

Furthermore, the trials and tribulations of AMR in the developed world is really just the tip of the iceberg. Far more worrisome is the potential impact in developing countries. 'The burden of infectious disease tends to be much higher in the developing world than the developed world, mainly because of water and sanitation issues,' confirms Tim Kelsall, senior research fellow at the Overseas Development Institute. Specifically, Kelsall refers to the way robust hygiene practices and sophisticated sewage and sanitation systems have prevented the spread of many once-common infections in developed countries. 'But those efforts are very much in their infancy in most of the developing world,' he explains. 'The antibiotics that treat those infections become pivotal to the lives of many millions of people. Because people are more vulnerable to infectious diseases, any kind of weakening in the strength of the drugs that can be used to treat those diseases becomes a graver problem.'

The worst-case scenario outlined by the 2016 *AMR review* – ten million deaths per year due to AMR – applied significantly to the developing world. 'Over the last ten years there's been a lot of action and a lot of concern in Europe and North America, because they have the data to understand what a big problem it is,' says Tayler. 'But the bulk of the deaths annually would be in Africa and in Asia – around four million each – and only a very small number in Europe. That's because they've got a much higher burden of infectious diseases at the moment, and their health systems are much less resilient and able to cope with it. So it is a huge problem globally, but very much for those countries.'

'AMR is a development issue,' insists Tim Jinks, head of the drug-resistant infections programme at the Wellcome Trust. 'But when I go out and engage with various stakeholders, it's far from obvious that this is the case.' Jinks warns that antimicrobial resistance could have major consequences that potentially reverse some significant developmental achievements and milestones of recent decades. 'We have to be very technocratic around this and focus on the sustainable development goals (SDGs), and where this phenomena of AMR undermines the progress that has been made on the SDGs. So we have to talk about it as a development issue, and where we can point to the fact the AMR threatens the ability to fulfil the health benefits that are related to development.'



Monitoring global progress on addressing AMR

This map series provides an overview of an analysis of a global country self-assessment survey on antimicrobial resistance conducted by the Food and Agricultural Organization of the United Nations (FAO), the World Organisation for Animal Health, and the WHO. The study is a step towards developing a global action plan in addressing antimicrobial resistance. Since the problem is not only related to human health, the study also looks at the field of plants and animals.

NEW DRUGS

The logical solution to bacteria becoming resistant to old antibiotics is to get some new ones. But this has proved to be easier said than done in recent years. The last new 'class' of antibiotics – groupings of biologically similar compounds, often derived from similar sources – to become available medically were launched in 1987 and nothing has emerged since.

'When I was a medical student, we didn't get worried about AMR because there were lots of new drugs being developed,' recalls Tayler. 'Since the 1980s, there have been almost no new classes of drugs. The pipeline's very, very empty, this is the real problem. And the reason that the pipeline is empty is partly because we've found all the best ones.' While a WHO report published last year identified 51 antibiotics currently in the testing phase, it estimated the chance of any reaching final approval at only 14 per cent, and stated that these antibiotics 'will add little to the already existing arsenal and will not be sufficient to tackle the impending AMR threat'.

As if the challenges of finding new antibiotics wasn't more difficult now that all the 'best ones' have already been found, one of the key reasons for this empty pipeline is the brittle economic model which leads to the development and eventual manufacturing of new drugs. Unlike in the development of other drugs, such as those required for chemotherapy, that often require long courses of treatment that will generate a handsome profit for drug developers, the prospective financial returns for developing new antibiotics is extremely small and far riskier. 'If somebody develops a fantastic new antibiotic next week, we'd say "Please don't use it very much, because we want to keep it reserved for resistance"', reveals Tayler. In these circumstances, it is perhaps understandable that few pharmaceutical companies feel it is worth investing in developing new antibiotics if they can rarely be used.

'Economists would call it a classic case of market failure,' says Lord Jim O'Neill, once chief economist for Goldman Sachs. 'Pharmaceutical companies, I rudely describe, as essentially being balance-sheet managers that happen to have the technical knowledge of producing and distributing drugs. They spend their whole life trying to manage the quarterly balance sheet, and they have – as many other companies do – different individual business units that have a return on capital target. If you think like that, antibiotics are never going to get you out of bed with excitement, because they're really expensive to research, and you can't sell them at any mad price that you'd like.' Developing new drugs was one of the 'ten commandments' for tackling AMR which emerged from the O'Neill review. Alongside such other commandments as new vaccines and rapid diagnostics, O'Neill argues there has since been 'an idiotic amount of talk, but zero progress'.

The approval of the antibiotic plazomicin, whose development was supported by the Wellcome Trust, for use in the treatment of drug-resistant urinary tract infections in the US in June this year, is an example of how funding and research does lead to results. But without new classes of antibiotics being found, over time it isn't difficult for bacteria to figure out how to make small mutations and develop resistance to these new drugs as well.

Farming

80

Percentage of national consumption of antibiotics by animal and livestock sectors in countries such as the US and Brazil

'More antibiotics are given to healthy animals than sick humans,' says Dr Liz Tayler, from the World Health Organization. 'Antibiotic abuse in the animal sector is a massive problem, and as middle income countries and emerging economies demand more meat, that's a very big worry.' Research shows that in some countries, as much as 80 per cent of national consumption of medically important antibiotics is in the animal sector, primarily for growth promotion in healthy animals.

'Some of these countries are big meat producers, and you can bump up profit margins if you pump your animals full of antibiotics, because that means you don't have to keep them in sanitary conditions – which are expensive to maintain,' adds Tim Kelsall at the Overseas Development Institute. 'This is the problem in the US, and – although there's not much data on this – there are suggestions that it's also a problem in places such as China.'

Colistin, once known as the so-called 'last line of defence' antibiotic, only to be used when all other antibiotics had failed, has now come up against bacteria it is ineffective against. In 2015, it was revealed that, following the irresponsible use of colistin as a growth promoter in livestock farming, a strain of bacteria with the mcr-1 gene (making it resistant to colistin) had been discovered in southern parts of China. It was the hammer blow experts had hoped never to hear, but feared it was coming one day. China has now banned the use of colistin for growth promotion in livestock farming.

The launch of Colombia's first national surveillance programme for measuring and controlling AMR in livestock shows how the animals' pivotal role in this issue could be reduced. Initially focused only on identifying antibiotic-resistant bacteria in chickens, and recognising which antibiotics were leading to the development of AMR in Colombia, the programme has seen AMR decrease over time, and is now being expanded into other livestock industries, as well as inspiring copycat programmes across Latin America.

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TECHNOLOGY RETURNS

Nevertheless, finding the next great antibiotic is the dream of biological chemists around the world. Like Fleming before them, many turn to the soil, where most current antibiotics were originally discovered. Unfortunately, the few microorganisms happy to grow in traditional lab environments, such as *Penicillium*, are running low. 'We can only readily culture about one per cent of microorganisms on the petri dish in the lab,' explains Kim Lewis, director of the Antimicrobial Discovery Center in the College of Science at Northeastern University in Boston, Massachusetts. 'One source of new antibiotics potentially would be uncultured bacteria, that make up the vast majority of biodiversity on the planet.'

By developing a new device known as the iChip, which is capable of growing colonies of uncultured bacteria in a controlled environment away from the petri dish, Lewis and his colleague Slava Epstein were able to study the resulting growths in search of new discoveries which may yet be the new penicillin. Around 30 such compounds were located, one of which really made them sit up and pay attention. 'The most interesting so far is called teixobactin,' reveals Lewis. 'It came from a very unusual bacteria, a new genus that we named *Eleftheria terrae*, which means "free earth".'

The discovery of teixobactin was published in a paper in *Nature* in January 2015, and quickly whipped international media into a frenzy, proclaiming it the first new antibiotic in nearly 30 years, and a saviour in the fight against AMR. Lewis is much more measured about his expectations. Nevertheless, he notes one particular characteristic which is generating significant optimism. 'We could not get any mutants resistant to teixobactin,' he explains. 'That was very surprising.' Teixobactin has so far effectively treated MRSA and numerous other antibiotic-resistant infections in mice, with no signs of developing resistance. Lewis believes this is due to the multiple angles of attack which teixobactin launches upon bacteria, making it very hard for any mutants to survive and multiply.

In an innocuous building overlooked by Lincoln Cathedral, steps are being taken to ensure the teixobactin discovery has an impact in the medical world. Dr Ishwar Singh and his team at the University of Lincoln have honed in on the exact amino acids required to make teixobactin so effective, enabling them to produce synthetic versions of it in the lab, without needing to wait for the natural bacteria to grow. 'The synthetic forms were not as potent as the natural ones, so we have dissected it,' explains Singh. 'We have found out how to increase the potency to be as good as the natural product – and even how we can exceed it, to make a superior molecule.'

In the middle of a lab full of whirring machines, test tubes, beakers, bottles, and various bizarre gadgets, a small Christmas-tree shaped machine contains a series of test tubes on each 'branch', each containing a bright white powder. These powders are all various derivatives of synthesised teixobactin, what is left when the solutions emerge from the synthesiser machine and are completely freeze-dried. Compared to the natural process, it is fast and cheap, making it potentially applicable for the real world of drug manufacturing.

As with the research in Boston, the synthetic antibiotic has been effective at killing several infections in mice and, again, as yet shows no signs of resistance. 'It is a quantum jump in my eyes,' says Singh. 'Translating from test tubes to the real bacteria infection, that's what we have achieved so far.'

Of course, there is a huge cost attached to sending any potential new drug to be put through clinical trials, so Singh and his colleagues (including a parallel team in Singapore) are rigorously testing their discovery to ensure it is up to the job. 'There is a very high cost on the clinical trial, that's why you need only your best molecules,' he explains. 'I am very optimistic. We have got the molecules which have got potential to become medicine one day, but a significant amount of work still remains to be done.'

At this stage, both Singh and Lewis insist all hopes should not pinned on teixobactin. Despite the brilliant potency it has shown so far, teixobactin isn't proving to be effective against gram-negative bacteria, one of the two types of pathogens that is equipped with an extra defensive membrane. This additional protection means it is gram-negative bacteria such as *E coli*. which are causing the most concern with regards to AMR, as opposed to more vulnerable gram-positive bacteria like MRSA.

'The Holy Grail is not so much to find a single compound that can fight gram-negative bacteria; it's to develop a discovery platform, an approach

that gives you reliable probability of discovering fresh compounds,' says Lewis. 'Discovering a single compound is good, but the attrition rate is substantial. A lot of compounds are not going to make it all the way to the end. What my lab is doing now is orienting our discovery development process to focus on compounds acting against gram-negative bacteria.'

OTHER SOLUTIONS

There is clearly more to overcoming the AMR challenge than simply finding one or two miracle antibiotics. In fact, there are plenty who argue that there is more to it than finding new drugs in general. 'That's part of the solution, but it's not the only part,' says O'Neill. 'Most importantly it's about reducing the demand for antimicrobials, particularly the inappropriate use. If you do that successfully, you can permanently shift the demand. Whereas, given the nature of what antimicrobial resistance is, even if you get new drugs, over a generation the bugs will develop resistance. It's not a permanent game-changer.'

Particularly concerning is the growth of unregulated, prescription-free antibiotic consumption since the turn of the millennium among the BRICS countries (Brazil, Russia, India, China and South Africa), developing nations with relatively rising incomes (increasing GDP per capita has been shown to correlate with increased antibiotic consumption). In 2000, the countries with the highest average antibiotic consumption per capita included the United States, France, New Zealand and Spain. By 2015, the highest rates were in countries such as Turkey, Tunisia, Algeria, and Romania.

For many, the challenge has been getting hold of enough antibiotics to cope with the threat of infectious diseases in the first place, so a rise in antibiotic consumption is, in some way, something to be celebrated. But from an AMR perspective, the news is far less rosy. 'You don't want to cut off people's access to drugs, because the effects will be very detrimental,' says Kelsall. 'But at the same time you need to find a way of regulating that supply, so that over time these drugs don't become useless.'

O'Neill emphasises the role that rapid diagnostics could play in the future, allowing GPs to avoid prescribing broad spectrum antibiotics by quickly diagnosing a patient's condition during the initial discussion, and being able to then assign a specific antibiotic to tackle just that condition. Being able to limit antibiotic consumption to the absolute bare minimum in this way could radically reduce the long-term risks.

'We think these things are like sweets,' says O'Neill. 'We've got to re-educate all of us to realise that, yes, they are one of the greatest inventions ever, but you only use them when there's a bacterial infection, and you only use them when you're sure that that's the case. Even then, you've got to be picking the right one for the right kind of bacterial infection.

> 'You need to find a way of regulating the supply, so that over time the drugs don't become useless'

The problem remains about more than just overprescription. The rampant use of antibiotics in livestock farming and/or leaching into the environment through wastewater remains of vital concern, and further avenues for these bacteria to needlessly develop resistance may yet make themselves apparent in the future. Nevertheless, from the perspective of the public, the key way to manage AMR has to be through the responsible consumption (or otherwise) of antibiotics when managing our own health.

Nevertheless, as well-meaning as domestic efforts to tackle AMR in countries such as the UK could be, there also need to be radical changes to the relationship between these drugs and the developing world, if unnecessary antibiotic consumption and subsequent AMR are to be reduced. The good news is that incremental changes are being made. For example, Tanzania's nationwide network of over 12,000 ADDOs (accredited drug dispensing outlets) has resulted in trained drug dispensers distributing antibiotics as and when they are necessary, a far cry from the casual, unregulated sales of the past. A similar story can be seen in South Africa, where antibiotic consumption has been reduced by providing specialised AMR training to many of the country's hospital pharmacists. Assigned with this duty, they can advise doctors and nurses with regards to the most appropriate usage of antibiotics.

CAUTIOUS OPTIMISM

The good news is that AMR is becoming more of a prevalent issue, which is itself crucial to stopping the spread of resistant bacteria globally, forming one of O'Neill's ten *AMR Review* commandments. Of the other nine, he highlights two which have seen progress he considers in line with the recommendations – a rise in the number of AMR research centres and microbiology researchers, and investments in early stage research and development. 'Actually, the progress has been as good as I could have dreamt,' he enthuses. Unfortunately, that leaves seven other commandments awaiting the time and attention they require.

The whole issue has jumped up several notches in importance since 2016, when it became just the fourth health issue to ever be recognised by the UN as a global threat. The UN Global Action Plan has seen the creation of an open-access database, in which different countries submit their strategies for tackling the AMR problem before it becomes a full-blown crisis. Similar to the Paris Agreement to combat climate change, the plan aims to synchronise actions and best practices across borders and multiple industrial sectors, to finally create a united front against the threat of AMR.

Wellcome's Tim Jinks talks about 'cautious optimism' regarding the efforts underway. 'AMR is something that has to be managed,' he emphasises. 'This isn't a single disease, and its not about disease eradication. It's about systems changes and how it is that we prevent and protect against infectious diseases.' Perhaps, with coordinated planning, Fleming's warning can be heeded, and his remarkable legacy saved. ●